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REVIEW

Therapeutic targeting of myeloid cells in liver fibrosis: Mechanisms and clinical prospects

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Abstract

Liver fibrosis, a hallmark pathological endpoint of chronic aging-related liver diseases, remains a clinical challenge with limited therapeutic options. In healthy liver, myeloid cells constitute <5% of total hepatic immune cells, primarily comprising tissue-resident Kupffer cells. However, during aging or chronic injury, bone marrow–derived myeloid cell recruitment increases by two- to threefold in murine fibrotic models, reaching 15%–20% of intrahepatic immune populations. These infiltrating myeloid subsets exhibit functional plasticity, dynamically differentiating into pro-inflammatory macrophages or fibrosis-promoting Kupffer-like cells, contingent upon chemokine gradients (e.g., CCL2/CCR2 axis) and damage-associated molecular patterns (DAMPs). This review systematically examines the regulatory mechanisms of myeloid cells in liver fibrogenesis, with particular emphasis on their developmental origins, hepatic recruitment dynamics, functional heterogeneity, and pathogenic contributions to fibrosis. Furthermore, signaling pathways involving myeloid cells in liver fibrosis and therapeutic approaches modulating their differentiation and recruitment are discussed in this review.

KEYWORDS
aging, hematopoiesis, immune microenvironment, liver fibrosis, myeloid cells

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1 | INTRODUCTION

The liver, a vital organ for detoxification and metabolism, is susceptible to chronic injuries (viral infections, toxins, metabolic stress), leading to fibrosis as a convergent pathological outcome.[1,2] Liver fibrosis, a hallmark pathological endpoint of chronic liver disease (CLD), is defined by excessive extracellular matrix (ECM) deposition and architectural remodeling. Sustained hepatic injury activates lysyl oxidase (LOX) family enzymes (e.g., LOXL2), which catalyze ECM cross-linking to form stable fibrous septa.[3] This progressive architectural distortion culminates in cirrhosis, characterized by severe complications, including portal hypertension, hepatic encephalopathy, and potential progression to hepatocellular carcinoma. Although liver transplantation serves as the gold-standard therapy for end-stage cirrhosis, its clinical application is constrained by donor shortages, immune rejection risks, and prohibitive costs.[4] The urgency of advancing hepatic fibrosis research is underscored by the escalating global prevalence of cirrhosis. CLDs collectively affect approximately 25% of the worldwide population, with hepatic fibrosis developing in nearly 20% of these cases.[5,6] This clinical progression culminates in cirrhosis, which has emerged as a major global health challenge. According to mortality statistics released by the World Health Organization (WHO) in 2024, cirrhosis-related complications now account for over 1.5 million deaths annually, further emphasizing the critical need for targeted therapeutic interventions.[7] Despite this significant disease burden, there remains a critical lack of effective therapeutic interventions capable of reversing established fibrosis. This therapeutic gap highlights the imperative need for in-depth investigations into the fundamental pathophysiological mechanisms driving fibrogenesis, which could inform the development of targeted antifibrotic strategies.

The hepatic immune microenvironment has been identified as a critical regulator of fibrosis pathogenesis. Single-cell sequencing results demonstrate that during liver injury or infection, there is a significant increase in the recruitment of myeloid cells to the liver, accompanied by phenotypic changes in their subsets.[8–10] Interactions between immune cells and cytokines during the transition from acute injury to chronic fibrosis present potential therapeutic targets for disrupting pro-fibrotic pathways.[11] Among immune cells, distinct subsets of hepatic macrophages exhibit dual functions, promoting both fibrosis progression and resolution. This review evaluates the roles of myeloid cells in sustaining hepatic immune homeostasis and driving disease progression. We analyze cellular and molecular mechanisms underlying myeloid cell behavior in physiological and pathological states, with a focus on immune niche remodeling, and assess therapeutic strategies that modulate myeloid cell activity to mitigate fibrosis.

2 | REGULATORY MECHANISMS OF HEPATIC MYELOID CELL IN LIVER FIBROSIS

2.1 | Origin and recruitment of hepatic myeloid cell

The liver harbors a unique immune network due to its dual blood supply (portal vein and hepatic artery), exposing it to gut-derived antigens and pathogens. There includes resident and recruited immune cells. Among them, myeloid cells, including macrophages, neutrophils, monocytes, eosinophils, and dentritic cells, are central immunoregulators.

Under normal physiological conditions, hematopoietic stem cells (HSCs) give rise to all mature blood cells through a tightly regulated differentiation process. This differentiation primarily follows two major lineages: the lymphoid lineage and the myeloid lineage. Initially, HSCs differentiate into common lymphoid progenitors (CLPs) and common myeloid progenitors (CMPs). Myeloid progenitors further diversify into granulocytes (including neutrophils, eosinophils, and basophils), monocytes/macrophages, erythrocytes, megakaryocytes/platelets, and dendritic cells (DCs), each playing distinct roles in immunity, oxygen transport, and tissue repair.[12] This highly orchestrated differentiation is governed by a combination of cell-intrinsic transcriptional programs and extrinsic signals from the bone marrow niche, including cytokine gradients and stromal cell interactions.[13] The detailed myeloid and lymphoid lineage differentiation pathways of HSCs are schematically illustrated in Figure 1.

In the context of hepatic fibrosis, the predominant myeloid cell populations are predominantly bone marrow–derived, with their quantitative and qualitative characteristics being directly governed by HSCs' differentiation propensity. The aging process induces functional deterioration in core metabolic organs, significantly elevating susceptibility to hepatic fibrosis, renal dysfunction, and cardiovascular pathologies.[14] This age-related deterioration is mechanistically linked to systemic alterations in hematopoiesis, particularly the development of myeloid-biased differentiation in HSCs, which operates in concert with chronic low-grade inflammation and mitochondrial dysfunction to drive tissue degeneration.[15,16] The pathological myeloid skewing of aged HSCs manifests through three interconnected phenomena: diminished lymphopoiesis leading to impaired adaptive immunity, exaggerated myelopoiesis resulting in expanded pro-inflammatory effector populations, and dysregulated cytokine production that perpetuates immune imbalance. This triad of hematopoietic dysfunction not only increases vulnerability to infections and hematological malignancies but also establishes a pro-fibrotic milieu that accelerates end-organ damage.[17]

At the molecular level, inflammation-induced nuclear factor kappa B (NF-κB) activation in aged HSCs orchestrates a transcriptional reprogramming of hematopoietic differentiation, characterized by suppression of lymphoid lineage determinants like Ikzf1 and concomitant upregulation of myeloid-specific factors, including Cebpa. This shift is further amplified by selective elevation of cell cycle regulators (Myc, Ccnb2) in myeloid progenitors, creating a self-reinforcing loop that drives excessive myeloid output.[18] Transplantation studies using aged marrow have conclusively demonstrated that myeloid-skewed HSCs autonomously propagate their pathological differentiation program to recipient animals, resulting in increased circulating myeloid cells and enhanced tissue infiltration by monocyte-derived macrophages regardless of the host's age. Importantly, these aberrant myeloid populations exhibit distinct pro-fibrotic polarization marked by excessive transforming growth factor β (TGF-β) production, directly contributing to ECM deposition and architectural distortion in target organs like the liver and lungs.[14,19]

The consequences of myeloid skewing extend beyond local tissue damage to encompass systemic metabolic dysregulation. The chronic

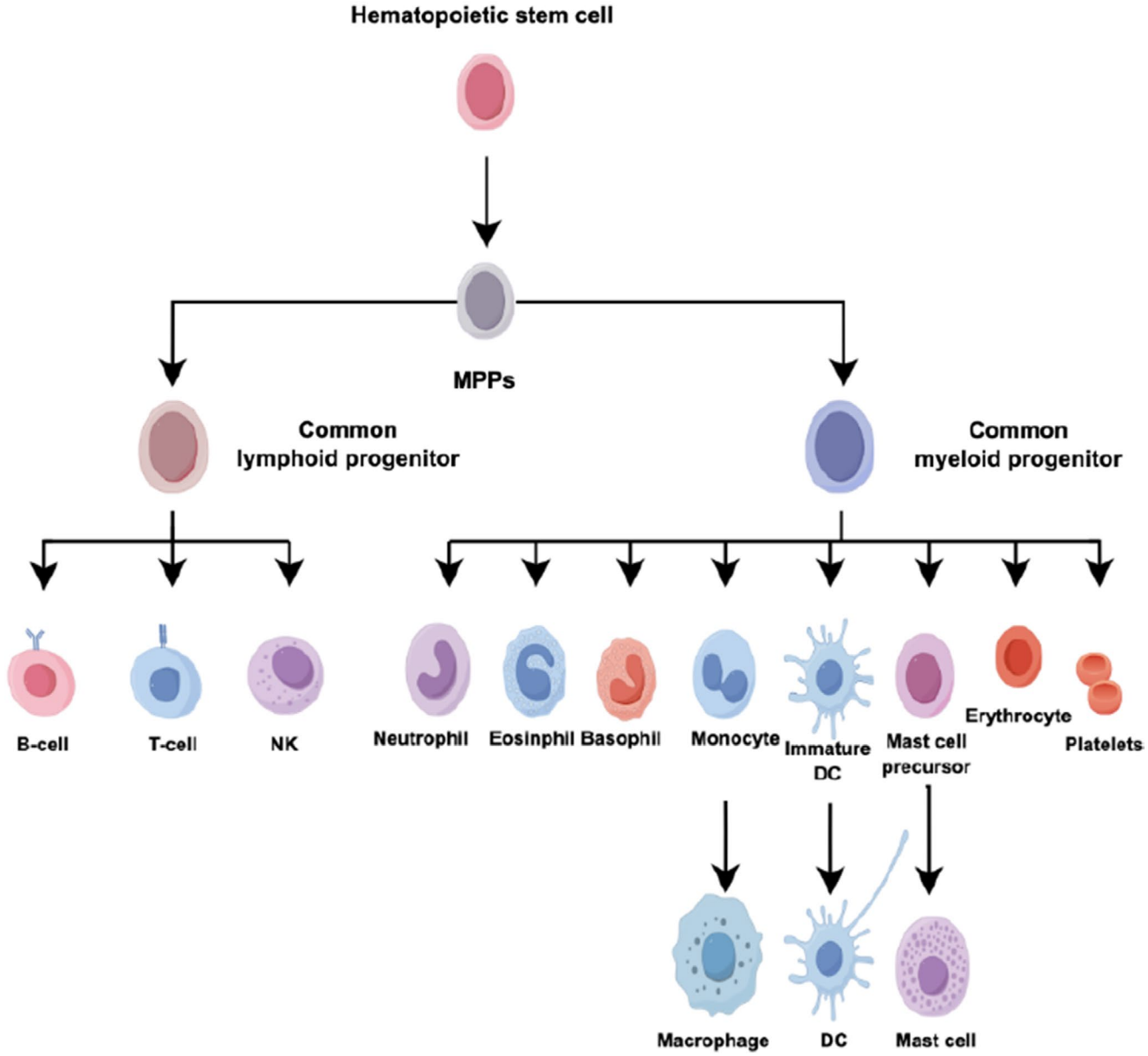

FIGURE 1 Differentiation lineage of hematopoietic stem cells (HSCs). HSCs primarily differentiate into two types of progenitor cells: common lymphoid progenitors and common myeloid progenitors. Lymphoid progenitors further develop into B cells, T cells, and natural killer (NK) cells. Myeloid progenitors differentiate into neutrophils, eosinophils, basophils, monocytes, immature dendritic cells (DCs), mast cell precursors, erythrocytes, and platelets. After migrating to tissues and organs, myeloid cells undergo further specialization: monocytes mature into macrophages, immature DCs become mature DCs, and mast cell precursors develop into mast cells, each performing distinct immune functions.

inflammatory state linked to myeloid-biased hematopoiesis accelerates the progression of age-related diseases, including coronary artery disease, congestive heart failure, stroke, chronic obstructive pulmonary disease, osteoporosis, and periodontitis,[20–22] while also contributing to insulin resistance and lipid metabolism disorders. These effects exacerbate comorbid conditions such as type 2 diabetes and obesity, which are frequently associated with progressive liver disease.[23–25] Epigenetic alterations, particularly the age-related decline in DNMT3A and TET2 function within hematopoietic stem and progenitor cells (HSPCs), further entrench myeloid bias by derepressing pro-inflammatory gene networks.[26] Together, these interconnected mechanisms create a perfect storm of immune dysfunction, metabolic disturbance, and fibrotic progression that underscores the central role of HSC aging in multiorgan pathology.[23]

2.1.1 | Monocytes

The recruitment of myeloid cells from bone marrow to the hepatic immune microenvironment represents a critical step in fibrotic pathogenesis, with monocyte-derived macrophages playing a central role. Monocytes are broadly categorized into two subsets distinguished by chemokine receptor profiles and surface marker expression.[9] Inflammatory monocytes in mice, characterized by high Ly-6C and

CD11b expression (equivalent to $CD14^+CD16^-$ monocytes in human), exhibit elevated CCR2 and low CX3CR1 levels. Under steady-state conditions, these Ly-$6C^{hi}$ monocytes typically constitute 2%–5% of circulating immune cells under homeostasis but rapidly mobilize to inflammatory sites upon stimulation. Bone marrow stromal cells, including mesenchymal stem cells (MSCs) and CXCL12-abundant reticular cells, respond to pathogen-associated molecular patterns through toll-like receptor (TLR) activation, triggering CCL2 release that facilitates Ly-$6C^{hi}$ monocytes egress via CCR2 binding.[27] The establishment of CCL2 chemotactic gradients, stabilized through interactions with endothelial glycosaminoglycans or transendothelial transport mediated by Duffy antigen receptor, directs monocyte trafficking to injured tissues.[28–30] In contrast, the nonclassical monocyte subset in mice (Ly-$6C^{lo}$) has low CCR2 and high CX3CR1 expression, corresponding to $CD14^+CD16^+$ monocytes in humans. These cells perform vascular surveillance by engaging endothelial CX3CL1 (fractalkine) through CX3CR1, enabling early pathogen detection and resolution of inflammation via anti-inflammatory mediators.[31,32]

2.1.2 | Neutrophil

Neutrophil recruitment follows distinct but equally regulated pathways, with these granulocytes being continuously produced in bone marrow at approximately 2×10^{11} cells per day under the regulation of granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor (G-CSF/GM-CSF), which is modulated by interleukin 17 (IL-17) (from γδT and NKT cells) and IL-23 (from tissue-resident macrophages and DCs).[33] Their maturation is transcriptionally controlled by PU.1 and C/EBPα.[34,35] During hepatic injury, neutrophils employ a unique CD44-hyaluronan-mediated adhesion mechanism to sinusoidal endothelia that differs from conventional integrin-dependent pathways. Liver sinusoidal endothelial cells (LSECs) express hyaluronan, which interacts with CD44 on neutrophils, facilitating their precise localization to inflammatory foci.[10] Besides, ATP released by necrotic hepatocytes activates the NLRP3 inflammasome via P2X7 receptor signaling, generating an intravascular chemokine gradient (e.g., CXCL2) that guides neutrophil migration.[36] Formyl peptides from necrotic cells further direct neutrophils to injury sites. Furthermore, the TLR4 ligand S100A9 protein secreted in hepatitis was a key regulator of hepatic CXCL2 expression and neutrophil recruitment.[37] Together, these carefully orchestrated recruitment mechanisms ensure the timely delivery of myeloid effectors to sites of liver injury while maintaining the capacity for both pro-inflammatory and resolution responses critical to fibrotic progression.

2.1.3 | Other cells

In the progression of liver fibrosis, nondominant myeloid cells play relatively minor roles and are recruited to the liver in smaller quantities. During hepatic injury, hepatocytes, stellate cells, and macrophages secrete the chemokine CCL11, which recruits eosinophils via CCR3 receptor binding.[38] Concurrently, IL-5 produced by Th2 cells and group 2 innate lymphoid cells (ILC2s) enhances eosinophilopoiesis in the bone marrow and promotes their migration to the liver.[39] In chronic liver inflammation, LSECs upregulate CXCL12 expression, facilitating the recruitment of $CXCR4^+$ basophils.[40–42] Activated hepatic stellate cells secrete stem cell factor (SCF) during fibrosis, driving the recruitment of mast cell (MC) progenitors through c-Kit receptor signaling. Necrotic hepatocytes release CXCL1, which attracts mature MCs via the CXCL1/CXCR2 axis.[43,44] The hepatic Flt3 ligand (Flt3L) supports the differentiation and migration of bone marrow–derived DC precursors to the liver.[45] Additionally, pathogen-associated molecules, such as lipopolysaccharide (LPS), activate the TLR4 pathway in hepatic macrophages, inducing the secretion of CXCL9 and CXCL10, which recruit CXCR3-expressing $CD103^+$ DCs to regulate the hepatic immune microenvironment.[46]

2.2 | Functional roles of hepatic myeloid cells in fibrogenesis

Hepatic myeloid cells exhibit remarkable heterogeneity and functional diversity, playing pivotal roles in maintaining immune homeostasis in the liver. Following hepatic injury, these cells are recruited to the liver and differentiate into effector populations, actively participating in immune responses and pathological processes. Their dynamic involvement represents a central mechanism in the progression of liver fibrosis. As summarized in Table 1, we provide a comprehensive classification of liver myeloid subsets along with their characteristic surface marker profiles.

2.2.1 | Macrophages

Liver macrophages consist of two major subsets: embryonic yolk sac–derived Kupffer cells (KCs) and monocyte-derived macrophages (MoDMs).[47] In healthy states, KCs constitute 80%–90% of hepatic macrophages and establish a specialized niche through pseudopod extensions that interface with parenchymal cells, including hepatic stellate cells, LSECs, and hepatocytes. These tissue-resident macrophages maintain immune surveillance via pattern recognition receptors (TLRs and scavenger receptors) and phagocytosis of pathogens/apoptotic debris.[48,49] As dominant antigen-presenting cells (APCs), KCs enforce immune tolerance by activating regulatory T cells (Tregs) while suppressing effector T-cell activation mediated by conventional APCs.[50] This tolerogenic function is reinforced during systemic exposure to low-dose particulate antigens, where KC-mediated antigen presentation induces $CD4^+$ T-cell anergy[51] and expands IL-10-producing populations,[52,53] leading to suppressed hepatic inflammation and establishment of tolerogenic immunity. By clearing pathogens (e.g., gram-positive bacteria) and senescent cells (e.g., erythrocytes, platelets), KCs reduce inflammatory triggers, thereby indirectly sustaining immune homeostasis.[54,55]

TABLE 1 Myeloid cell subsets.

Class	Subsets	Makers	Specific features
Macrophage	Kupffer cell	F4/80$^+$, CLEC4F$^+$, TIM4$^+$	Antigen-presenting, clearance of debris, regulation of lipid and iron
	Ly-6C^{hi}MoDM	CD11b$^+$, F4/80$^+$, Ly-6C^{hi}	Pro-inflammatory cytokines and chemokines secretion
	Ly-6C^{lo}MoDM	CD11b$^+$, F4/80$^+$, Ly-6C^{lo}	Matrix resolution
	LAM	F4/80+, CD68+, CD11b+, CD9$^+$, TREM2$^+$, CD36$^+$	Regulate lipid metabolism, efferocytosis
Monocyte	Ly-6C^{hi} monocytes	CCR2$^+$, CX3CL1$^-$, Ly-6C^{hi}	Inflammatory response
	Ly-6C^{hi} monocytes	CCR2$^-$, CX3CL1$^+$, Ly-6C^{lo}	Inflammatory response subsidence
Neutrophil	-	CD11b$^+$, Ly-6G$^+$	Phagocytosis, degranulation, NETs
Eosinophil	-	CD11b$^-$, CD11b$^-$, SiglecF$^+$	Protective function
Basophil	-	FcεRI$^+$, CD11b$^+$, CD44$^+$	Type 2 immunity
Mast cell	-	c-Kit$^+$, FcεRI$^+$	Ductular reaction
LDC	CD103$^+$DC	Lin$^-$, PDCA1$^-$, CD11c$^+$, MHCII$^+$, CD103$^+$, CD11b$^+$	Resemble lymphoid tissue resident-DC
	CD103$^-$DC	Lin$^-$, PDCA1$^-$, CD11c$^+$, MHCII$^+$, CD103$^-$, CD11b$^+$	Derived from both resident DC precursor and monocyte lineage
	pDC	Lin$^-$, PDCA1$^-$, CD11c$^+$	IFN-I production and antiviral response
	LDC precursor	Lin$^-$, CD11c$^+$, MHCII$^+$, SIRPa^{lo}	LDC proliferation in situ

Abbreviations: LDC, hepatic dendritic cell; NETs, neutrophil extracellular traps.

Under pathological conditions such as liver fibrosis, KCs' functionality undergoes significant transformation. Niche alterations lead to loss of characteristic macrophage features and impaired bacterial surveillance in sinusoids. In response to persistent pathogen exposure, CD44-mediated recruitment of bone marrow–derived monocytes initiates the formation of KC-like syncytia within collateral vessels, which replenish the KC pool through CD36-dependent cellular adhesion and fusion mechanisms, restoring bacterial clearance capacity.[56,57] Damage-associated molecular patterns (DAMPs) activate KCs to adopt a pro-inflammatory phenotype, secreting CXCL2 (neutrophil chemoattractant), tumor necrosis factor α (TNF-α), and CCL2/CCL5, which drive neutrophil influx and monocyte recruitment, perpetuating fibrosis.[58,59] This chemokine amplification loop critically drives fibrotic progression through sustained monocyte infiltration.

Infiltrating monocytes differentiate into macrophages, the dominant pro-fibrotic population.[60] Guided by chemokines (CCL2, CX3CL1), these macrophages phagocytose cellular debris and mediate antigen presentation, linking innate and adaptive immunity.[61,62] Additionally, macrophages process and present antigens to T and B lymphocytes, bridging innate and adaptive immune responses. Their secretion of bioactive molecules—cytokines, chemokines, complement proteins, and enzymes—further modulates inflammatory and immune cascades.[61] Ly-6C$^+$ (mouse)/CD14$^+$ (human) monocytes are recruited to injury sites via CCL2, differentiating into pro-inflammatory macrophages.[63] These cells secrete TGF-β and platelet-derived growth factor (PDGF) to directly activate hepatic stellate cells and synergize TNF-α/IL-1β with the NF-κB-Smad axis to upregulate collagen synthesis.[64] PDGF activates ERK/PI3K-Akt pathways in hepatic stellate cells, promoting proliferation and migration. TGF-β, the most potent pro-fibrotic cytokine, drives ECM deposition.[65]

During resolution phases, Ly-6C^{lo} monocytes or IL-4-polarized M2 macrophages dominate, degrading ECM via matrix metalloproteinases (MMPs). Mechanosensitive Piezo1 channels enhance efferocytosis and IL-10 secretion,[66] whereas STAT6-PPARγ signaling mediates lipid metabolic reprogramming, fostering anti-inflammatory responses and matrix remodeling.[67,68]

A specialized macrophage subset, termed lipid-associated macrophages (LAMs), critically modulates hepatic inflammation and fibrosis progression in fatty liver disease. In healthy livers, LAMs localize predominantly near bile ducts but dynamically accumulate in steatotic regions during metabolic dysfunction-associated steatotic liver disease (MASLD) or obesity.[69,70] Characterized by the expression of surface markers CD9$^+$/TREM2$^+$/CD36$^+$, LAMs exhibit functional heterogeneity, transitioning between pro-inflammatory and tissue-reparative phenotypes depending on disease stage and microenvironmental cues.[71] Under pathological conditions such as MASLD and cirrhosis, LAMs primarily originate from CCR2$^+$/CX3CR1$^+$ monocyte recruitment, driven by chemotactic signals from lipid-burdened hepatocytes and stromal cells.[72] Additionally, local proliferation of LAM precursors (e.g., Ms4a7$^+$ cells) and KC-mediated niche modulation further contribute to LAM pool expansion, with KC depletion impairing both recruitment and differentiation processes.[73]

TREM2, a central regulator of LAM activity, governs lipid uptake, efferocytosis, and inflammatory modulation via pathways involving APOE and PPAR-γ.[71] Activation of TREM2 by sphingosine-1-phosphate

(S1P), released from apoptotic hepatocytes, enhances efferocytotic clearance of lipid-laden debris, thereby mitigating lipotoxicity and preserving hepatic homeostasis.[74] Conversely, hepatocyte-derived ANGPTL8 interacts with the leukocyte receptor Pirab/LLRB2, promoting monocyte-to-LAM differentiation and amplifying pro-fibrotic signaling through collagen deposition and hepatic stellate cell activation.[75]

Functional polarization of LAMs dictates their divergent roles in disease progression. During early metabolic dysfunction-associated steatohepatitis (MASH), $CCR2^+$ monocyte-derived LAMs secrete pro-inflammatory cytokines (e.g., TNF-α, IL-1β), exacerbating neutrophil infiltration and parenchymal injury.[70] In advanced stages, scar-associated macrophages (SAMs), a LAM subset marked by elevated SPP1 (osteopontin) expression, drive fibrosis by activating hepatic stellate cells and depositing ECM components.[76,77] $Trem2^+$ LAMs also regulate hepatocyte lipid metabolism through mitochondrial pathways, such as the miR-106b-5p-Mfn2 axis, which attenuates steatosis by enhancing mitochondrial fusion and lipid oxidation.[78] These findings underscore LAMs as pivotal regulators of hepatic inflammation resolution and fibrotic remodeling, highlighting their potential as therapeutic targets in metabolic liver diseases.

2.2.2 | Neutrophils

Constituting 1%–2% of circulating immune cells under homeostasis, are rapidly mobilized postinjury via G-CSF/GM-CSF.[79,80] Activation mechanisms involve pattern recognition through TLR2/9, immunoglobulin Fc receptors, and complement system components.[81,82] Neutrophils eliminate pathogens via three principal effector mechanisms: phagocytic engulfment, reactive oxygen species generation, and neutrophil extracellular trap (NET) formation.[33,83,84] Notably, NET components, including DNA-protein complexes, granular enzymes (myeloperoxidase, neutrophil elastase, MMP-9), and modified histones, demonstrate pro-fibrotic potential. Mechanistic studies reveal that hepatic stellate cell activation occurs through dual signaling cascades: TLR9-mediated NF-κB activation and TGF-β-dependent Smad phosphorylation, ultimately facilitating ECM remodeling.[85] The pathological effects are amplified through histone-induced TLR4/MyD88 signal transduction and NET-derived chemotactic factors (CXCL1/CXCL8), which establish a self-perpetuating inflammatory microenvironment conducive to sustained fibrogenic processes.[86]

2.2.3 | Eosinophils

Eosinophils, traditionally associated with antiparasitic immunity and allergic responses,[87] are increasingly recognized for their regulatory roles in inflammation resolution and tissue repair. IL-33 released by damaged sinusoidal endothelial cells activates eosinophils, which secrete CCL24 to recruit additional eosinophils via a feedforward loop.[88,89] Activated eosinophils mitigate excessive inflammation by suppressing IFN-γ via IL-4/IL-13 and promote repair through heparin-binding epidermal growth factor (HB-EGF) release from macrophages, mediated by p38-COX-NF-κB signaling.[90] This dual functionality underscores eosinophils as emerging modulators of hepatic inflammation resolution and regenerative processes.

2.2.4 | Dentritic cells

As specialized APCs, DCs execute critical immunological functions encompassing antigen capture, processing, and presentation, coupled with lymphoid organ homing and cytokine-mediated coordination of innate/adaptive immunity.[91,92] Hepatic DCs (LDCs) under homeostatic conditions maintain an immunotolerant phenotype characterized by functional immaturity.[93] During liver injury, DC precursors expand locally under the stimulation of GM-CSF or FLT3L, whereas circulating DCs may also replenish the hepatic DC pool.[94–96] In chronic liver injury, pro-inflammatory LDCs dominate, promoting fibrosis by secreting IL-6 and TNF-α, which activate hepatic stellate cells and drive collagen deposition.[97] Contrastingly, acute injury induces protective LDC subpopulations that mitigate tissue damage through neutrophil apoptosis regulation, effectively attenuating parenchymal necrosis. Current research limitations stem from overlapping phenotypic markers with monocyte-derived cells and context-dependent plasticity, necessitating advanced single-cell analyses to delineate precise regulatory mechanisms in hepatic fibrogenesis.

2.2.5 | Mast cell and basophils

Although MCs and basophils represent a minor population among hepatic immune cells, they play significant roles in liver pathological processes. MCs are closely associated with cholangiocyte injury, as cholangiocyte-derived insulin-like growth factor-1 (IGF-1) promotes MC migration to the liver, where they accumulate around damaged bile ducts and release histamine, thereby inducing ductular reaction (DR), cholestasis, and liver fibrosis.[98] MCs directly activate hepatic stellate cells by releasing histamine, tryptase, and TGF-β1, driving their transdifferentiation into myofibroblasts. Furthermore, MCs exacerbate the fibrotic microenvironment through vascular endothelial growth factor (VEGF)- and fibroblast growth factor-2 (FGF-2)-mediated sinusoidal capillarization.[99] Basophils primarily participate in type 2 immune responses by producing IL-4 and IL-13, which promote hepatic stellate cell activation and collagen synthesis.[100] Additionally, basophils recognize IgE-antigen complexes via FcεRI, triggering the release of pro-inflammatory mediators such as histamine and LTB4, thereby aggravating liver injury.[101]

Emerging evidence reveals that hepatic macrophages originating from bone marrow progenitor cells undergo functional specialization in response to local tissue signals, demonstrating remarkable adaptability through their capacity to adopt distinct activation states characterized as pro-inflammatory (M1) or immunoregulatory (M2) populations.[102] The M2 phenotype displays additional heterogeneity with four recognized subtypes (M2a–d), each demonstrating unique functional characteristics.[103]

Macrophage polarization dichotomy is fundamentally regulated by differential arginine processing pathways: classically activated M1 macrophages preferentially express inducible nitric oxide synthase (iNOS) to catalyze the conversion of arginine into citruttine and nitric oxide, whereas alternatively activated M2 macrophages predominantly use arginase-1 (Arg1) to metabolize arginine into ornithine and urea.[104] This metabolic divergence establishes arginase pathway modulation as a promising therapeutic target for macrophage functional reprogramming.

Cellular bioenergetic pathways significantly influence inflammatory programming, with M1 macrophages demonstrating glycolytic dependency compared to the oxidative phosphorylation (OXPHOS) preference of M2 phenotypes.[105] Metabolic pathway switching has been shown to mediate phenotypic interconversion, as evidenced by reduced pro-inflammatory cytokine production following glycolytic inhibition. The glycolytic master regulator HIF-1α not only enhances glycolytic flux and pentose phosphate pathway activity but also promotes M1 polarization.[106–108] Its activation is modulated by multiple metabolic signals, including TCA cycle intermediates (succinate/citrate), mechanistic target of rapamycin complex (mTORC1) signaling, and pyruvate kinase M2 (PKM2) activity.[109–111] Interestingly, neutrophil-derived oxidative stress can induce AMPK activation in macrophages, inhibiting mTOR-mediated signaling to facilitate metabolic shift from glycolytic M1 toward OXPHOS-dependent M2 states.[112]

Lipid metabolic reprogramming exerts bidirectional effects on macrophage polarization. Although M2 polarization associates with PPAR-mediated fatty acid oxidation (FAO) potentiation through RIPK3 signaling, FAO inhibition fails to completely reverse M2 characteristics, suggesting compensatory mechanisms.[113,114] Paradoxically, FAO can trigger inflammasome activation in M1 macrophages, highlighting context-dependent effects. Lipid synthesis, conversely, correlates with pro-inflammatory responses.[114–116] Inhibiting lipid synthesis while enhancing catabolism promotes M2 polarization and alleviates inflammation.[117,118] The mTORC1-SREBP-1a axis maintains crucial phagocytic functions through regulated lipid synthesis, illustrating the dual regulatory roles of lipid metabolism in macrophage biology.[119,120]

Amino acid handling further contributes to polarization dynamics, where glutamine metabolism supports M2 activation via α-ketoglutarate-mediated epigenetic regulation and FAO induction.[121] Glutamine-depleted microenvironments trigger compensatory glutamine synthetase upregulation, though the functional consequences require further investigation. Serine metabolic pathways exhibit context-dependent regulation, supporting M1-associated IL-1β production through phosphoglycerate dehydrogenase signaling and NLRP3 inflammasome activation.[122,123] Serine synthesis inhibition shifts macrophages toward M1 polarization via JAK/STAT signaling, whereas its upregulation promotes M2 phenotypes.[124,125] However, serine metabolism's role in inflammasome activation remains context-specific.

This metabolic network complexity underscores the intricate relationship between nutrient utilization and immune cell function, suggesting therapeutic potential in targeting key metabolic nodes (glycolysis, FAO, amino acid pathways) to rebalance inflammatory and reparative responses in hepatic pathophysiology and systemic inflammatory disorders.

Within the inflammatory milieu, KC-derived IL-6 initiates paracrine signaling through IL-6 receptor/gp130 complexes on neighboring hepatocytes and macrophages, triggering STAT3 activation that orchestrates dual biological processes.[126,127] STAT3 drives hepatocyte dedifferentiation to support regeneration[128] and regulates macrophage polarization by suppressing the pro-inflammatory Ly-6C^{hi} phenotype while promoting the generation of reparative Ly-6C^{lo}macrophages.[129] During distinct phases of injury, STAT3 and STAT6 exhibit stage-specific synergy: STAT3 responds to early inflammatory signals, whereas STAT6 mediates M2 polarization in later stages, collectively inhibiting Ly6C^{hi} monocyte activity and fostering tissue repair.[130,131] Concurrently, TGF-β signals through Smad2/3 in the resolution phase to induce M2 macrophage polarization and suppress Ly-6C^{hi} monocyte recruitment, thereby attenuating inflammation and promoting fibrosis regression.[132–134] The transcription factors IRF4 and PPARγ form a complex that amplifies M2-associated gene transcription and restrains the inflammatory activity of Ly-6C^{hi} monocytes, further enhancing reparative responses.[135,136] Th2 cytokine signaling through IL-4/IL-13-STAT6 axes further stabilizes M2 polarization states.[137]

Chromatin dynamics and epigenetic modifications fundamentally regulate macrophage functional adaptation in disease contexts. Nutritional stress in NASH pathogenesis induces AP-1/EGR-mediated enhancer landscape reorganization in KCs, disrupting LXR-dependent homeostatic programming and triggering phenotypic conversion marked by Trem2/CD9 overexpression, ultimately resulting in KC depletion and monocyte-derived macrophage infiltration.[138] These recruited macrophages demonstrate fibrotic niche-adapted epigenomic signatures through convergent chromatin accessibility patterns. Mechanistic studies reveal STAT3 cooperates with chromatin modifier Arid1a to engage H3K27ac-marked regulatory elements, activating tissue-repair enhancers (e.g., Arg1/Ym1) while silencing Ly-6C^{hi}-associated inflammatory loci.[139–141] DNA methylation dynamics also contribute to phenotype regulation, with DNA demethylases like TET2 potentially modulating macrophage plasticity during tissue repair, though mechanistic details remain to be elucidated.[142,143]

This integrated signaling-epigenetic axis underscores the adaptability of hepatic macrophages to microenvironmental cues, balancing inflammatory resolution and regenerative responses in liver pathophysiology. We have schematically depicted the recruitment of myeloid cells to the liver under pathological conditions and their specific mechanisms in promoting both the progression and regression of hepatic fibrosis, as detailed in Figure 2.

3 | THERAPEUTIC STRATEGIES TARGETING MYELOID CELLS

Targeted therapeutic approaches for liver fibrosis based on molecular mechanisms can be broadly categorized into three strategies: inhibition of myeloid cell production and recruitment, suppression of myeloid cell-related pro-fibrotic signaling cascades, and macrophage phenotype reprogramming.

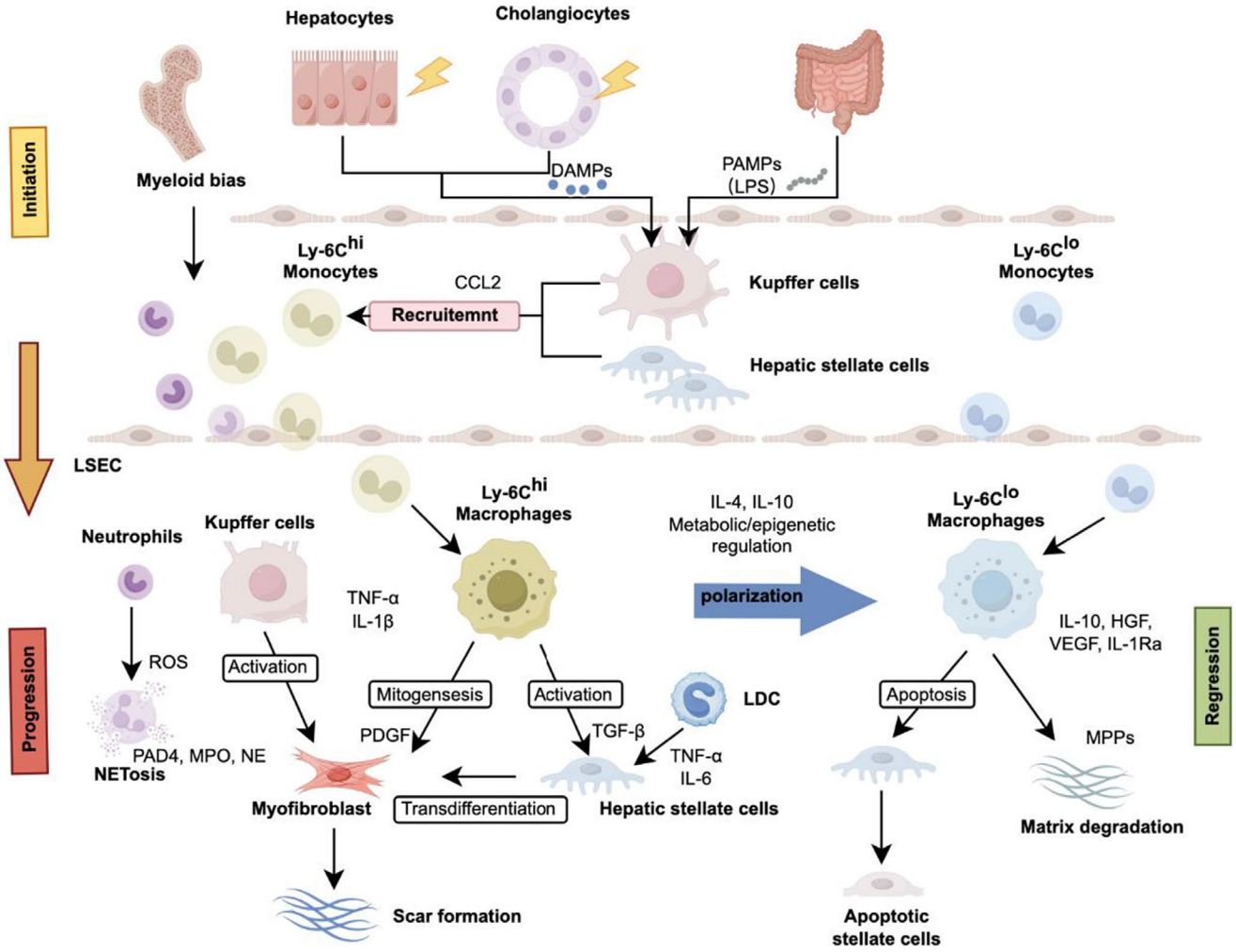

FIGURE 2 Mechanisms of myeloid cells in liver fibrosis progression. Myeloid bias in hematopoietic stem cells, damage-associated molecular patterns (DAMPs) released by injured hepatocytes and cholangiocytes, and gut-derived pathogen-associated molecular patterns (PAMPs, e.g., LPS) collectively drive alterations in the hepatic immune microenvironment. DAMPs and PAMPs activate Kupffer cells to initiate inflammatory responses. Kupffer cells and hepatic stellate cells jointly secrete factors that recruit Ly-6C^{hi} monocytes and neutrophils. These pro-inflammatory myeloid cells secrete cytokines within the liver microenvironment, further activating hepatic stellate cells and promoting collagen deposition. During fibrosis resolution, Ly-6C^{lo} monocyte-derived macrophages facilitate collagen degradation and induce apoptosis of activated hepatic stellate cells.

3.1 | Targeting myeloid-biased hematopoiesis

The myeloid skewing of aged HSCs (my-HSCs) represents a fundamental driver of age-related hepatic fibrosis, positioning the targeting of myeloid differentiation a potential upstream approach for modulating the liver's immune microenvironment. Age-associated DNMT3A dysfunction, a critical DNA methyltransferase responsible for silencing inflammatory genes, exacerbates myeloid-mediated hepatic pathology. The loss of DNMT3A activity leads to derepression of pro-inflammatory genes (e.g., IL-1α), thereby amplifying hepatic inflammatory responses and accelerating fibrotic progression. Pharmacological strategies aimed at restoring DNMT3A function could potentially rebalance hematopoietic output by epigenetically suppressing IL-1α overproduction, thereby interrupting the self-perpetuating cycle of inflammation-driven fibrosis.[23] Recent investigations have demonstrated that Oridonin inhibits DNMT3A R882 mutation-driven clonal hematopoiesis and leukemia by inducing apoptosis and necroptosis, suggesting its potential therapeutic value for ameliorating myeloid skewing-related peripheral organ pathologies. Furthermore, emerging evidence indicates that selective elimination of my-HSCs by targeting surface antigen combinations (CD150/NEO1/CD41/CD62p) can effectively restrict the generation of pro-inflammatory myeloid cells while promoting lymphopoiesis, consequently enhancing immune competence in aged hosts.[144] Therapeutic modulation of the hematopoietic differentiation trajectory, either through inhibition of inflammation-induced NF-κB hyperactivity or by rebalancing key transcription factors (upregulating lymphoid factor Ikzf1 while suppressing myeloid determinant Cebpa), may offer potential for reversing myeloid bias at its origin. Although clinically effective pharmaceuticals targeting myeloid skewing remain to be developed, this approach holds considerable therapeutic promise for age-related fibrotic disorders.

3.2 | Inhibition of myeloid cell recruitment

The recruitment of inflammatory monocytes can be attenuated by targeting key chemokine pathways such as CCL2-CCR2, CCL1-CCR8, and CXCL10-CXCR3. Monoclonal antibodies against these chemokines or their receptors effectively block signal transduction, thereby preventing monocyte infiltration into the liver.[145] For instance, the CCR2/CCR5 dual antagonist Cenicriviroc (CVC) has demonstrated efficacy in ameliorating liver fibrosis in patients with nonalcoholic steatohepatitis.[146,147] Similarly, inhibition of G-CSF suppresses neutrophil differentiation in bone marrow, subsequently reducing inflammatory responses.[148,149] Certain compounds, such as curcumin, exert indirect effects by attenuating KC activation and subsequent chemokine secretion, leading to decreased Ly-6C^{hi} monocyte infiltration and prevention of hepatic fibrosis.[150,151] Additionally, reversing myeloid bias in HSCs represents a potential therapeutic target, which may concurrently exert antiaging and antifibrotic effects. However, no clinical studies have yet investigated this approach for treating liver fibrosis.

3.3 | Suppression of myeloid cell-mediated profibrotic signaling

The TGF-β pathway represents a critical therapeutic target, as it serves as both a key activator of hepatic stellate cells and a mediator of systemic aging through macrophage signaling.[14] TGF-β inhibition significantly reduces expression of fibrotic markers, including TIMP-1, collagen types I/IV, α-SMA, and endothelin-1.[152] Anti-inflammatory cytokine antagonists, particularly anti-TNF-α monoclonal antibodies (e.g., infliximab) and IL-1 receptor antagonists (e.g., anakinra), show potential in reversing hepatic stellate cell activation. Preclinical studies have revealed context-dependent efficacy of IL-1β antagonism, which reduces hepatic stellate cell proliferation in vitro.[153] Enhancement of IL-10 signaling exerts dual therapeutic effects through coordinated immunomodulatory mechanisms. Mechanistically, IL-10 elevation drives macrophage phenotypic switching toward restorative M2-like polarization while simultaneously inducing senescence in activated hepatic stellate cells via paracrine regulation, simultaneously decelerating fibrogenesis and promoting tissue repair.[154,155] These findings underscore the multifactorial nature of fibrosis treatment, which requires integration of regenerative, immunomodulatory, and direct antifibrotic strategies while balancing efficacy, safety, and translational potential.[156,157]

Macrophage polarization offers another promising therapeutic avenue due to the functional plasticity of these cells, with MSC therapies from diverse tissue sources showing clinical promise.[158] MSC mechanisms encompass secretome-mediated hepatocyte regeneration via IGF-1/PI3K/AKT/β-catenin axis activation and sinusoidal endothelial repair through VEGF-A/Flt1-HB-EGF/HGF cross talk.[159,160] Additionally, MSC-mediated immunomodulation through IL-4 and IL-10 secretion promotes macrophage polarization from pro-fibrotic Ly-6C^{hi} to pro-resolving Ly-6C^{lo} phenotypes, thereby suppressing production of TGF-β, PDGF, TNF-α, and IL-1β. This phenotypic switch effectively inhibits hepatic stellate cell activation and reduces oxidative stress. In murine models of liver fibrosis, splenectomy has been shown to promote ERK1/2 phosphorylation in macrophages, facilitating their conversion to the Ly-6C^{lo} phenotype and subsequently ameliorating hepatic inflammation and fibrosis. Clinical investigations are currently exploring the therapeutic potential of autologous monocyte-derived macrophages that have been ex vivo polarized toward a reparative phenotype for liver fibrosis treatment.[161,162] Further therapeutic options are systematically summarized in Table 2.

4 | CONCLUSIONS AND PERSPECTIVES

We summarize current knowledge on liver myeloid cells, including their origins, recruitment, and functional roles in both physiological and fibrotic conditions. We highlight key regulatory mechanisms governing myeloid cell behavior and discuss their implications for liver fibrosis progression.

Current therapeutic strategies primarily focus on three approaches: blocking pathological myeloid recruitment via chemokine axis targeting, correcting myeloid dysfunction through small-molecule inhibitors of key signaling pathways (TGF-β/STAT3/IL-6), and rebalancing macrophage polarization via stem cell therapies or epigenetic editing. Although MSC-based therapies show promise in modulating macrophage phenotypes and enhancing matrix degradation, clinical translation remains limited by challenges in cellular homing efficiency and functional persistence. Several targeted agents against pro-fibrotic myeloid pathways have entered phase 2/3 trials, showing 20%–35% reduction in hepatic collagen content compared to placebo. However, the interconnected nature of fibroinflammatory signaling networks necessitates stage-specific therapeutic selection. For instance, early-stage patients (F0–F2) may benefit more from CCR2 blockade, whereas advanced fibrosis (F3–F4) might require combinatorial TGF-β/STAT3 inhibition. The specific antifibrotic efficacy of therapeutic agents targeting distinct molecular pathways remains to be rigorously validated through additional clinical trials. Despite promising preclinical findings regarding their mechanisms of action in hepatic fibrosis resolution, the clinical translation of these targeted therapies requires comprehensive verification in well-designed multicenter studies with standardized endpoints.

Especially, accumulating evidence suggests that HSC myeloid skewing represents a fundamental cause of immune dysregulation in liver fibrosis. The myeloid bias of senescent HSCs leads to a decline in the body's anti-inflammatory capacity, resulting in increased susceptibility to peripheral organ damage and a state of persistent chronic inflammation. Consequently, aging is frequently associated with elevated incidence and mortality rates of various chronic diseases, including liver fibrosis. Recent studies have demonstrated that targeted clearance of senescent hematopoietic cells can reverse systemic aging, wherein the proportion of myeloid

TABLE 2 Potential therapy targeting myeloid cells in liver fibrosis.

Target/pathway	Drug/intervention
Myeloid bias	Surface antigen combinations (CD150/NEO1/CD41/CD62p) (preclinical)
DNMT3A	Oridonin (preclinical)
CCR2/CCR5 antagonist	Cenicriviroc mesylate (phase 3) Gemcabene calcium (phase 2) WXSH-0213 (preclinical)
G-CSF/GM-CSF	Talimogene laherparepvec (approved for listing) Pexastimogene devacirepvec (phase 3) BS 001 (phase 3) ORIENX 010 (phase 2) SYNOV1.1 (phase 1) mSJ 650 (preclinical) NCT03415698
TLR4/NF-κB signaling, CCL2 secretion	Curcumin (phase 2)
TGF-β/Smad pathway	Fresolimumab (phase 2)
TNF-α antagonist	Infliximab (approved for listing) WO2023147029 (preclinical)
IL-1R antagonist	CUD 005 (phase 1) Anakinra (approved for listing)
IL-4-IL-13R antagonist	Stapokibart (approved for listing)
IL-11R antagonist	Interleukin 11 antagonist (Boehringer Ingelheim) (preclinical) LASN-01 (phase 2)
LPAR1 antagonist	Admilparant (phase 3)
PDGFR modulator	BOT-191 (preclinical) ATH-001 (preclinical) KBP-7018 (preclinical) 68Ga-BOT1712 (preclinical) Sorafenib Tosylate (approved for listing)
TLR4/MyD88 inhibitor	Resatorvid (preclinical)
LOXL2 inhibitor	Simtuzumab (phase 3)
Macrophage polarization (mesenchymal stem cells)	MSCs from allogeneic bone marrow (NCT01741090) MSCs from autologous adipose (NCT02297867) MSCs from menstrual blood (NCT01483248)
Stem cell therapy	Bone marrow–derived mononuclear cells and $CD133^+$ cells (NCT01120925) Autologous $CD34^+$stem cells (NCT00147043)

Abbreviations: G-CSF/GM-CSF, granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor; IL, interleukin; NF-κB, nuclear factor kappa B; PDGFR, platelet-derived growth factor receptor; TGF-β, transforming growth factor β; TLR, toll-like receptor; TNF-α, tumor necrosis factor α.

cells within the immune microenvironment plays a pivotal regulatory role.[144,163] Preclinical models demonstrate that genetic ablation of myeloid transcription factors (e.g., PU.1 knockdown) reduces liver collagen deposition.[35] This underscores the therapeutic potential of intercepting myeloid differentiation trajectories during early liver injury. Clinically, the established association between clonal hematopoiesis (CHIP mutations: DNMT3A, TET2) and increased cirrhosis risk warrants enhanced surveillance of liver pathology in hematologic disorders.[26] By fundamentally reprogramming the hepatic immune niche through precision targeting of myeloid ontogeny, these strategies offer transformative potential to concurrently halt fibrotic progression and restore immune homeostasis.

In conclusion, the myeloid-biased differentiation trajectory of HSCs has emerged as a critical pathogenic determinant in hepatic fibrogenesis. Targeting the upstream dysregulation in HSC lineage commitment may enable immunomodulatory reprogramming of the hepatic niche, thereby disrupting the pro-fibrotic cascade at its origin. Preclinical studies indicate that restoring balanced myeloid-lymphoid output through HSC-directed interventions could ameliorate pathological immune cell infiltration in fibrotic livers, particularly by modulating KC polarization and monocyte-derived macrophage dynamics. Future investigations should prioritize multiomics profiling of tissue-resident immune cells to identify conserved molecular checkpoints governing HSC-immune cross talk. Such mechanistic insights may pave the way for precision therapies combining senolytic agents with microenvironment-modulating biologics, ultimately fostering innovative therapeutic paradigms that address both cellular senescence and maladaptive immunity in CLDs.

AUTHOR CONTRIBUTIONS

Yue Wang: Conceptualization; validation; visualization; writing – original draft. **Yiming Liu:** Visualization; writing – review and editing. **Dan Chen:** Visualization; writing – review and editing. **Leiming Liu:** Supervision; visualization; writing – original draft; writing – review and editing. **Leimin Sun:** Supervision; validation; writing – review and editing. **Lingling Zhang:** Conceptualization; funding acquisition; visualization; writing – original draft; writing – review and editing.

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Lingling Zhang is an editorial board member of Animal Models and Experimental Medicine (*AMEM*) and a corresponding author of this article. To minimize bias, she was excluded from all editorial decision making related to the acceptance of this article for publication.

ETHICS STATEMENT

None.

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